Eastern Association for the Surgery of Trauma

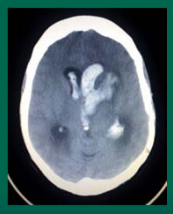
28th Annual Scientific Assembly

Sunrise Session 5
Emergent Reversal of Bleeding Associated with Novel Anticoagulants

January 14, 2015
Disney's Contemporary Resort
Lake Buena Vista, Florida

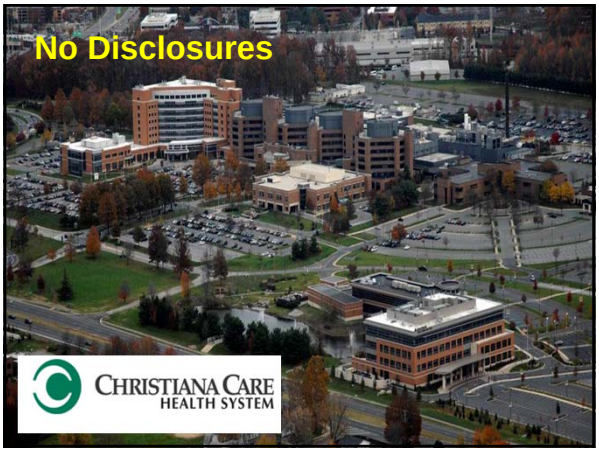
Emergent Reversal of Bleeding Associated with Anticoagulants

Mark Cipolle, MD, PhD, FACS, FCCM
Medical Director Trauma Program
Christiana Health Care System
Wilmington, DE



CHRISTIANA CARE HEALTH SYSTEM

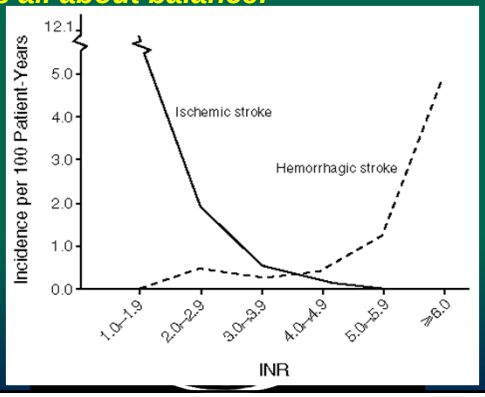
No Disclosures



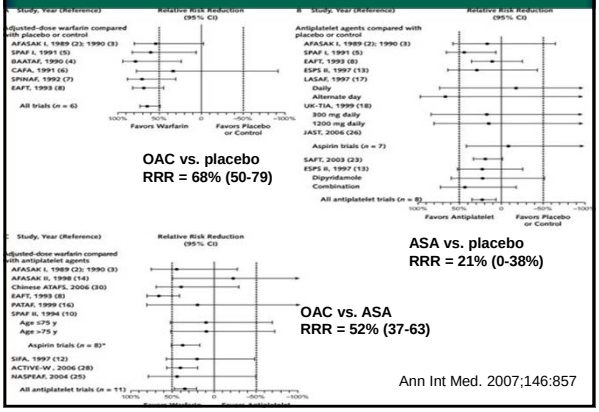
Outline

- Balancing risk: thrombosis vs. bleeding
- Review of PCCs
- Phase 3 trial PCC-4 vs FFP for warfarin-related bleeding
- Antiplatelet reversal
- New Anticoagulants
  - Bleeding complications
  - Animal and in vitro studies
  - Human studies
  - Strategies for urgent reversal
- Resumption of AT and AC

It's all about balance!



Risk Reduction of Ischemic Stroke in Atrial Fibrillation



OAC vs. placebo
RRR = 68% (50-79)

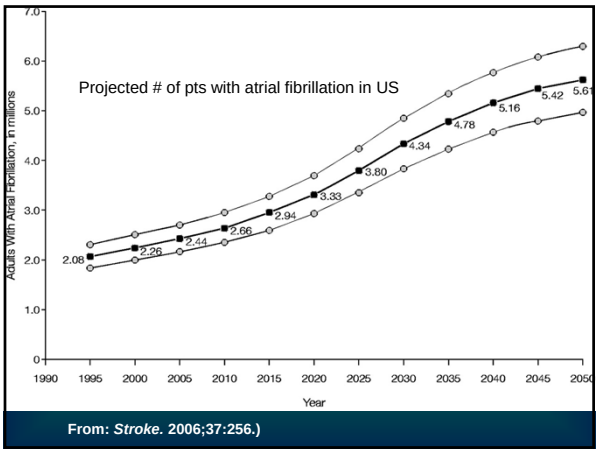
ASA vs. placebo
RRR = 21% (0-38%)

OAC vs. ASA
RRR = 52% (37-63)

Ann Int Med. 2007;146:857

Risk of ICH During Anticoagulation

- Overall incidence in clinical trials is generally < 1% per year and most trials are < 0.5%
- Increases significantly with INR > 4
- So with well controlled INR, stroke risk always exceeds ICH and by about 10 fold when get to intermediate stroke risk.



From: *Stroke.* 2006;37:256.)

ACCP Recommendations for VKA Reversal

- 2008: For immediate reversal, we **suggest** treatment with fresh frozen plasma, or another prothrombin concentrate in addition to low-dose IV or oral vitamin K **(Grade 2C)**
- 2012: we suggest rapid reversal of anticoagulation with 4-factor PCC rather than with plasma **(Grade 2C)**

Holbrook A, et al. *Chest.* 2012;141(2 suppl):e152S-e184S

Prothrombin concentrate complexes (PCCs)

Role of prothrombin complex concentrates in reversing warfarin anticoagulation: A review of the literature

Cindy A. Leissinger,[1]* Philip M. Blatt,[2] W. Keith Hoots,[3] and Bruce Ewenstein[4]

Am J Hematology 2008;83:137-143

TABLE I. PCCs for Warfarin Reversal: Coagulation Factor Composition

	FII	FVII	FIX	FX
3-Factor PCCs				
Preconativ[a]	84 U	–	100 U	84 U
Konyne[a]	152 U	16 U	100 U	152 U
Factor IXa[a]	Unavailable	–	Unavailable	Unavailable
Prothrombinex HT[b]	100 U	–	100 U	100 U
Bebulin[c]	120 U	13 U	100 U	139 U
Profilnine SD[c]	148 U	11 U	100 U	64 U
Cofact[d]	~75 U	~25 U	100 U	~75 U
4-Factor PCCs				
Beriplex P[e]	128 U	68 U	100 U	152 U
Prothrombex T[f]	100 U	85 U	100 U	100 U
Proplex T[g]	50 U	400 U	100 U	50 U
Octaplex[d]	44–152 U	36–96 U	100 U	72–120 U
PPSB-HT[g]	100 U	100 U	100 U	100 U
Unknown				
Prothromplex[a]	Unavailable	Unavailable	Unavailable	Unavailable

Role of prothrombin complex concentrates in reversing warfarin anticoagulation: A review of the literature

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Am J Hematology 2008;83:137-143

- **14 published studies**
  - **3 prospective randomized**
  - **4 prospective non-randomized**
  - **1 case control**
  - **6 retrospective reviews**
- **Effective in correction of elevated INR**
  - **Faster than vitamin K and FFP**
  - **Essentially free of thromboembolic complications**
  - **Wide array of dosing**
  - **May add rFVIIa to 3 component PCCs**
  - **Data correlating rapidity of correction of elevated INR to clinical outcome is lacking**

Anti-inhibitor coagulant concentrates (aPCCs)

- **"bypass" therapy for hemorrhagic disorders due to inhibitors, i.e., bypass need for factors VIII and IX**
- **PCCs that have been activated *in vitro***
  - **Increase content of activated and precursor vit-K dependent factors**
- **FEIBA and Autoplex T**
- **Indicated for bypass therapy in patients with acquired inhibitors**
- **Contain II, VII, IX, and X**

PCC-4 (KCentra®) for urgent reversal of warfarin-related bleeding

Correction of INR and coagulation factor levels in a randomized clinical trial of four-factor prothrombin complex concentrate (4F-PCC) *versus* plasma for urgent vitamin K antagonist reversal

[1]Majed A. Refaai, [2]**Joshua N. Goldstein**, [3]Truman J. Milling, [4]Henry C. Foehl, [4]Bruce Hug, [5]Ravi Sarode

[1]University of Rochester Medical Center, Rochester NY; [2]Massachusetts General Hospital, Boston, MA; [3]University Medical Center at Brackenridge, Dell Children's Medical Center, Austin TX; [4]CSL Behring, King of Prussia, PA; [5]UT Southwestern Medical Center, Dallas, TX, USA

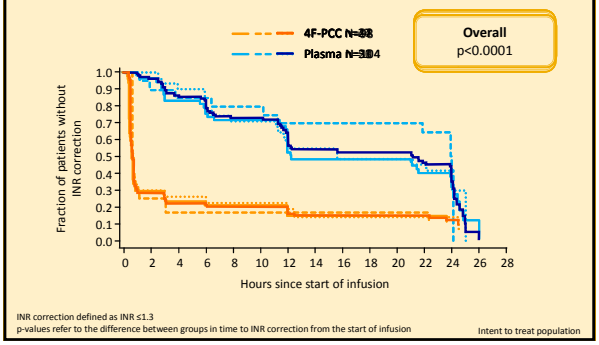
Background and study design
presented at ACEP 2012

A phase IIIb randomized controlled trial comparing a **4-factor PCC** (4F-PCC; Beriplex® P/N, CSL Behring) with **plasma**

- Patients (≥18 years) who received vitamin K antagonists (VKA) and experienced an **acute major bleeding** event were randomized (1:1) to receive **4F-PCC** (N=98) or **plasma** (active control; N=104)
- Patients were stratified by baseline INR (2 to <4; 4 to 6; >6) and weight into **three dose groups** per intervention

4F-PCC, four-factor prothrombin complex concentrate; INR, international normalized ratio — Intent to treat population

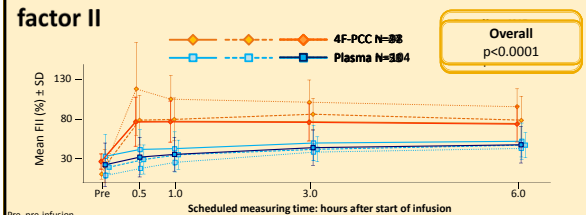
Patients who received 4F-PCC achieved INR correction faster than those who received plasma



INR correction defined as INR ≤1.3
p-values refer to the difference between groups in time to INR correction from the start of infusion

Intent to treat population

4F-PCC rapidly replaced vitamin K-dependent factor II



Pre, pre-infusion
p-values refer to the difference between groups at 30 minutes after the start of infusion

Intent to treat population

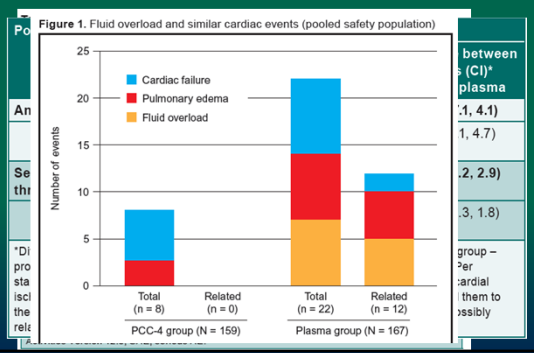
Conclusion

4F-PCC was **more successful** at **early INR reversal** and **coagulation factor repletion** than plasma

Integrated safety analysis of a 4-factor prothrombin complex concentrate versus plasma in Phase III clinical trials

Ravi Sarode,[1] Truman J. Milling,[2] Majed A. Refaai,[3] Antoinette Mangione,[4] Billie L. Durn,[4] Joshua N. Goldstein[5]

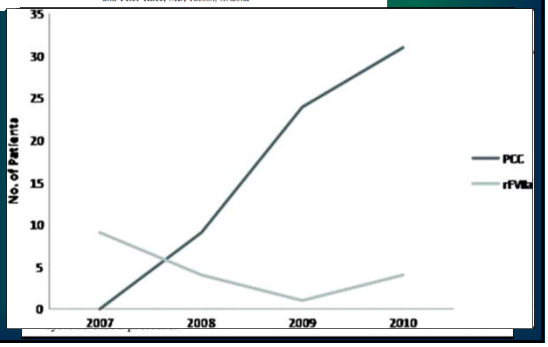
[1]UT Southwestern Medical Center, Dallas, TX; [2]University Medical Center at Brackenridge, Dell Children's Medical Center, Austin, TX; [3]University of Rochester Medical Center, Rochester, NY; [4]CSL Behring, King of Prussia, PA; [5]Massachusetts General Hospital, Boston, MA, USA



Prothrombin complex concentrate: An effective therapy in reversing the coagulopathy of traumatic brain injury

Bellal Joseph, MD, Pantelis Hadjizacharia, MD, Hassan Aziz, MD, Narong Kulvatunyou, MD, Andrew Tang, MD, Viraj Pandit, MD, Julie Wynne, MD, Terence O'Keeffe, MD, Randall S. Friese, MD, and Peter Rhee, MD, *Tucson, Arizona*

J Trauma 2013;74:24



Reversing anti-platelet agents

ACCP Recommendations for Reversal of Antithrombosis for Surgery or Invasive Procedures (8th edition, 2008)

- **For patients receiving aspirin, clopidogrel or both, are undergoing surgery and have excessive or life-threatening perioperative bleeding, we suggest transfusion of platelets or administration of other prohemostatic agents (Grade 2C).**

Normalization of platelet reactivity in clopidogrel-treated subjects.

Vilahur, et al. J Thromb Haemost. 5:82-90, 2007.

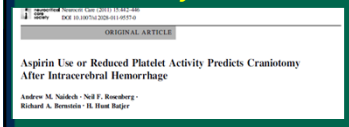
- 11 healthy volunteers
- ASA (325mg load then 81mg) + clopidogrel (300 or 600 load then 75mg)
- Administration of platelets resulted in normalized platelet function by assay

Ivascu, et al. J Trauma. 2008

Table 5 Comparison of Those Receiving Platelets and Those not Receiving Platelets

	No Platelets, N = 69	Platelets Transfused, (1st 24 hour) N = 40	*p*
Age	76.8 ± 9.9	78.2 ± 10.5	0.473
Gender	38M:31F	23M:17F	0.806
GCS	13.7 ± 2.8	13.5 ± 3.0	0.676
ISS	20.3 ± 6.7	23.4 ± 9.8	0.183
OR	8/69 (12%)	9/40 (23%)	0.137
Initial CT Grade			
Grade 1	23	47	
Grade 2	5	12	0.266
Grade 3	6	4	
Grade 4	6	6	
Mortality	9/69 (13%)	11/40 (28%)	0.064

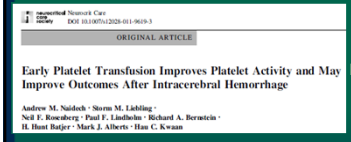
Platelet Activity and Non-Trauma ICH


ORIGINAL ARTICLE

Aspirin Use or Reduced Platelet Activity Predicts Craniotomy After Intracerebral Hemorrhage

Andrew M. Naidech · Neil F. Rosenberg · Richard A. Bernstein · H. Hunt Batjer

Neurocritical Care 2011;15:442


ORIGINAL ARTICLE

Early Platelet Transfusion Improves Platelet Activity and May Improve Outcomes After Intracerebral Hemorrhage

Andrew M. Naidech · Storm M. Liebling · Neil F. Rosenberg · Paul F. Lindholm · Richard A. Bernstein · H. Hunt Batjer · Mark J. Alberts · Hau C. Kwaan

Neurocritical Care 2011; online


Reduced Platelet Activity Is Associated With Early Clot Growth and Worse 3-Month Outcome After Intracerebral Hemorrhage

Andrew M. Naidech, MD, MSPH; Borko Jovanovic, PhD; Storm Liebling, BA; Rajeev K. Garg, MD; Sarice L. Bassin, MD; Bernard R. Bendok, MD; Richard A. Bernstein, MD, PhD; Mark J. Alberts, MD; H. Hunt Batjer, MD

Stroke 2009;40:2398

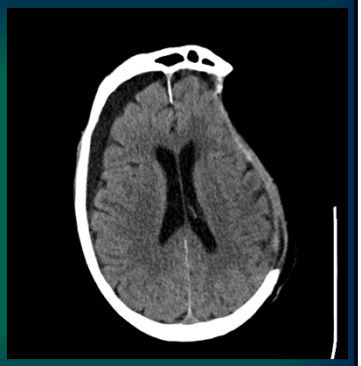
AABB Recommendation 2014

- **We cannot recommend for or against the administration of platelets for correction of bleeding in patients receiving antiplatelet therapy.**
  - **Grade 3C recommendation**

In press, Ann Int Med

The new anticoagulants

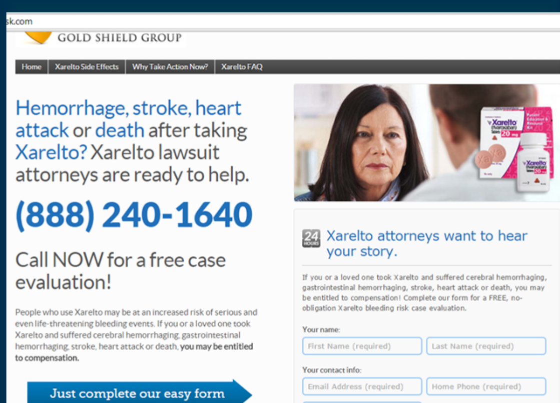
- 87 year old man on dabigatran for afib slipped on the ice going to the gym
- PT/INR and aPTT NORMAL
- TT > 180
- Urgent craniectomy



Pharmacokinetic Comparison: New Oral Anticoagulants

	Dabigatran	Rivaroxaban	Apixaban
Target for activity	Thrombin (II)	Anti-Xa	Anti-Xa
Prodrug	Yes	No	No
Bioavailability	6%	> 80%	> 50%
Time to peak Cp	2 hr	3 hr	3 hr
Half-life	14-17 hr	9 hr	9-14 hr
Dosing interval	Once/Twice daily	Once-daily	Twice daily

Gross PL et al. Arterioscler Thromb Vasc Biol 2008;28:380-6



Comparison of bleeding rates between TSOACs and warfarin: atrial fibrillation

- Randomized trials
  - Major bleeding = 2-3% per year with TSOAC
  - ICH = 0.1 to 0.5% per year with TSOAC
- "Real world" N > 50,000
  - Dabigatran vs. warfarin
    - Major bleeding: 1.6 vs 3.5 per 100,000 pt days
    - ICH: 0.8 vs 2.1 per 100,000 pt days

N Engl J Med 2013; 368:1272.
Lancet 2014; 383:955.
J Am Coll Cardiol 2014; 63:2141
Eur Heart J 2014; 35:1873

Comparison of bleeding rates between TSOACs and warfarin: VTE

- Meta analysis of 5 trials
  - N= 24,555
  - Bleeding rates with TSOACs
    - Fatal 0.06%
    - Non fatal ICH 0.09%
    - GI bleed 0.35%
  - **RR compared to warfarin = 0.5 (0.41-0.88)**

J Thromb Haemost 2014; 12:320

Management of bleeding and reversal strategies for oral anticoagulants: Clinical practice considerations

Am J Hosp Pharm
Nov 1, 2013

EDITH A. NUTESCU, WILLIAM E. DAGER, JAMES S. KALUS, JOHN J. LEWIN III, AND MARK D. CIPOLLE

Table 2.
Various Laboratory Tests To Consider When Concerned About Bleeding With Warfarin and Target-Specific Oral Anticoagulants (TSOAs)[22-24,a]

Laboratory Test	Warfarin	Dabigatran	Rivaroxaban	Apixaban	Comments
SCr and CBC with platelets	Potentially useful	Potentially useful	Potentially useful	Potentially useful	Monitor serum calcium concentration if transfusion is used
INR or PT	Potentially useful; value increased	Potentially useful; value increased; use central laboratory because point-of-care test can give much higher values	Potentially useful; value increased	Potentially useful; value increased	PT may be considered because INR may not be calibrated for the TSOAs; PT more responsive to factor Xa inhibitors than to dabigatran; limited ability to quantify amount of drug
aPTT	Potentially useful; value somewhat increased	Potentially useful; value increased, but aPTT response flattens at higher serum drug concentration	Potentially useful; value increased	Potentially useful; value increased	aPTT more responsive to dabigatran than to factor Xa inhibitors; limited ability to quantify amount of drug
TT	Clinical use limited	Potentially useful; very sensitive at low concentration but not useful at higher concentration	Inadequate measure	Inadequate measure	Limited ability to quantify amount of dabigatran
ECT	Clinical use limited	Potentially useful if available; potential ability to quantify amount of drug present	Inadequate measure	Inadequate measure	Limited availability; potential quantitative test
Diluted TT	Clinical use limited	Potentially useful if available; potential ability to quantify amount of drug present	Inadequate measure	Inadequate measure	Lack of standardization and potential differences in measured results among laboratories; may have limitations at low dabigatran concentration
Chromogenic antifactor Xa assay	Inadequate measure	Inadequate measure	Potentially useful; value increased	Potentially useful; value increased	Limited availability; nonstandardized; results may vary among laboratories where available

SCr = serum creatinine, CBC = complete blood count, INR = International Normalized Ratio, PT = prothrombin time, aPTT = activated partial thromboplastin time, TT = thrombin time, ECT = ecarin clotting time.

The NEW ENGLAND JOURNAL of MEDICINE

Cotton, McCarthy, Holcomb
NEJM 2011, 365:2039

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CORRESPONDENCE

Acutely Injured Patients on Dabigatran

N Engl J Med 2011; 365:2039-2040 | November 24, 2011

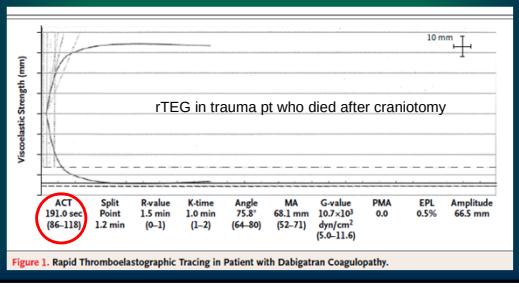


Figure 1. Rapid Thromboelastographic Tracing in Patient with Dabigatran Coagulopathy.

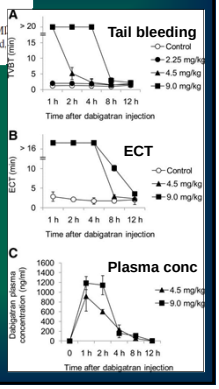
Animal and in vitro studies

Hemostatic Therapy in Experimental Intracerebral Hemorrhage Associated With the Direct Thrombin Inhibitor Dabigatran

Wei Zhou, MD*; Sönke Schwarting, MD*; Sergio Illanes, MD; Arthur Liesz, MD; Moritz Middelhoff, MSc; Markus Zorn, PhD; Martin Bendszus, MD; Sabine Heiland, PhD; Joanne van Ryn, PhD; Roland Veltkamp, MD

Stroke 2011;42:3594

- Mouse head injury model (striatal collegenase injection)
- Compared 4-PCC (KCentra®) to FFP and rFVIIa



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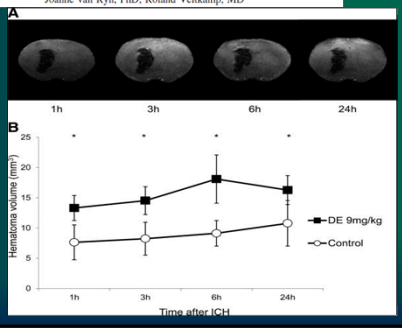

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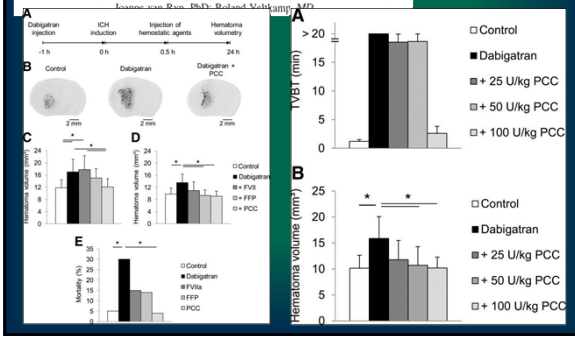

Partial Reversal of Dabigatran Effect by a Prothrombin Complex Concentrate in a Cell-Based Model of Thrombin Generation

Maureane Hoffman, Zoya Volovyk and Dougald M. Monroe
Duke University and The University of North Carolina Medical Centers, Durham and Chapel Hill, NC

- **In vitro model**
  - **Platelet rich plasma (6 donors)**
  - **Added to monocytes pretreated with endotoxin to stimulate tissue factor**
  - **Monitor thrombin generation with CAT®**

Partial Reversal of Dabigatran Effect by a Prothrombin Complex Concentrate in a Cell-Based Model of Thrombin Generation

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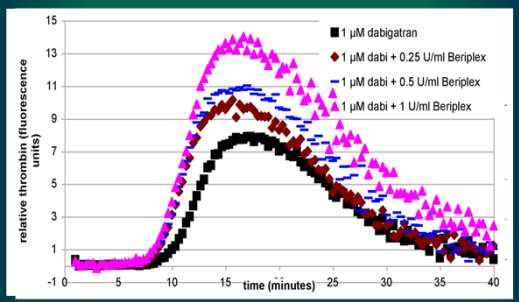

PCC reversal of dabigatran in rabbit model

Pragst I, et al. J Thromb Haemost. 2012;10(9):1841-8.

- Methods
  - Anesthetized, kidney incision
  - Dabigatran 0.4mg/kg
  - PCC doses of 20, 35, or 50 IU/kg vs. placebo
- Results
  - Dose related reduction in hemorrhage from 29 mL to 5.4 mL (95%CI = 2.21-8.67/10 IU/kg, p=0.002)
  - At 50 IU/kg blood loss was fully normalized
  - Increasing PCC doses shortened median time to hemostasis from 20.0 to 5.7 min (p < 0.001)
  - Rate of hemostasis nearly tripled with each 10 IU/kg of PCC dose
- Conclusion
  - This 4 factor PCC shows potential as an agent for reversing effects of dabigatran

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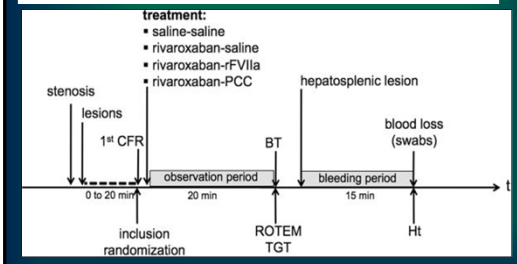
Evaluation of Prothrombin Complex Concentrate and Recombinant Activated Factor VII to Reverse Rivaroxaban in a Rabbit Model

Anesthesiology 2012;116:94

Anne Godier, M.D., Ph.D.,* Anastasia Miclot, M.Sc.,† Bernard Le Bonniec, Ph.D.,‡
Marion Durand, M.D., Ph.D.,§ Anne-Marie Fischer, M.D., Ph.D.,# Joseph Emmerich, M.D., Ph.D.,
Catherine Marchand-Leroux, Ph.D.,** Thomas Lecompte, M.D., Ph.D.,††
Charles-Marc Samama, M.D., Ph.D., F.C.C.P.‡‡



Evaluation of Prothrombin Complex Concentrate and Recombinant Activated Factor VII to Reverse Rivaroxaban in a Rabbit Model

Anesthesiology 2012;116:94

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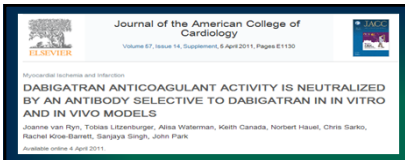
Marion Durand, M.D., Ph.D.,§ Anne-Marie Fischer, M.D., Ph.D.,# Joseph Emmerich, M.D., Ph.D.,
Catherine Marchand-Leroux, Ph.D.,** Thomas Lecompte, M.D., Ph.D.,††
Charles-Marc Samama, M.D., Ph.D., F.C.C.P.‡‡

- Rivaroxaban at 10mg/kg
  - Increased blood loss and ear bleeding
  - Conventional and TEG clotting times
  - Decreased thrombin generation
- Neither rFVIIa or PCC had effect on blood loss
- rFVIIa reduced ear bleeding time
- Both rFVIIa and PCC partially corrected clotting times
- Neither rFVIIa and PCC caused thrombosis

FEIBA in animal studies

- Corrected anticoagulant effect of rivaroxaban in primates
  - Gruber et al. ASH Annual Meeting Abstracts 2008;112:3825
- Reversed rivaroxaban effects in rat model
  - Perzborn et al. Pathophysiol Haemost Thromb 2008;36:A40


Journal of the American College of Cardiology

Volume 57, Issue 14, Supplement, 5 April 2011, Pages E1130

Myocardial Ischemia and Infarction

DABIGATRAN ANTICOAGULANT ACTIVITY IS NEUTRALIZED BY AN ANTIBODY SELECTIVE TO DABIGATRAN IN IN VITRO AND IN VIVO MODELS

Joanne van Ryn, Tobias Litzenburger, Alisa Waterman, Keith Canada, Norbert Hauel, Chris Sarko, Rachel Kroe-Barrett, Sanjaya Singh, John Park

Available online 4 April 2011.

- Boehringer Labs (US and Germany)
- Monoclonal mouse antibodies
- Inhibition of anticoagulant activity via diluted thrombin time
- Humanized and optimized
- Tested in human plasma in vitro and in rats ex vivo

- Results
  - Clone 22 with high potent and specific Kd of 34 pM to dabigatran
  - Complete inhibition of dabigatran both in human plasma and whole blood
  - Also complete inhibition in ex vivo model

(r)-antidote

- PRT064445, a recombinant antidote to anti Xa drugs
  - In rat bleeding model: Completely corrected blood loss associated with fondaparinux and almost completely reversed rivaroxaban

Miyares M and Davis K. Am J Health Syst Pharm 2012;69:1473.

Human data

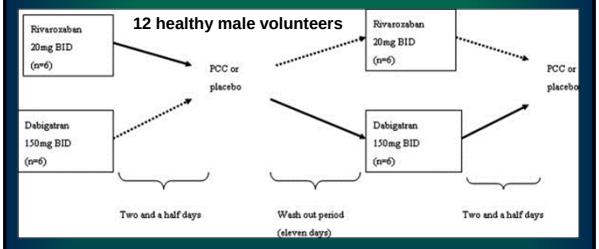
Reversing Dabigatran with FEIBA
Dager and Roberts, UC Davis
Poster #867

- 67 yo man with afib/rvr
- Last dabigatran dose 7h prior to cardiac ablation, also heparin 5000 for procedure
- Transeptal perforation!!
- Percardiocentesis
- 4.5L blood loss
- Rx with protamine 100mg and FEIBA 3156 units (26U/kg) over 15 mins
- Other resus fluids
- Bleeding slowed immediately and stopped before FEIBA infusion completed!
- Thrombin time remained > 80 seconds

Reversal of Rivaroxaban and Dabigatran by Prothrombin Complex Concentrate
A Randomized, Placebo-Controlled, Crossover Study in Healthy Subjects

Elise S. Eerenberg, MD; Pieter W. Kamphuisen, MD; Meertien K. Sijpkens, BSc; Joost C. Meijers, PhD; Harry R. Buller, MD; Marcel Levi, MD

Circulation 2011; 124:1573-1579



CHRISTIANA CARE HEALTH SYSTEM

Reversal of Rivaroxaban and Dabigatran by Prothrombin Complex Concentrate

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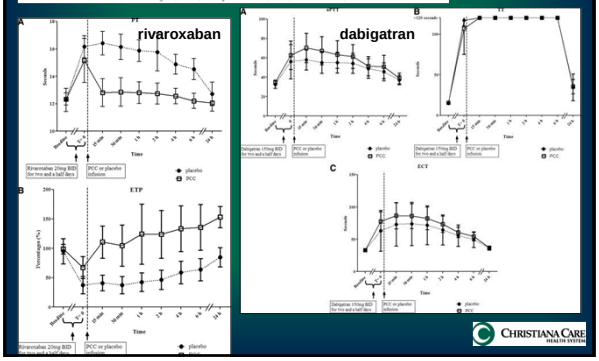


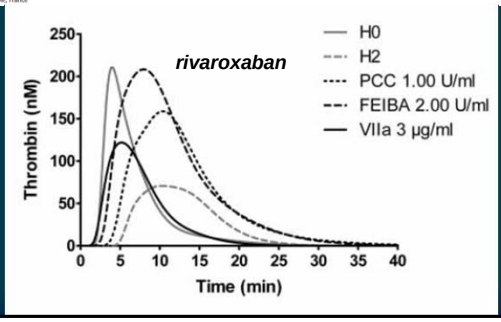
CHRISTIANA CARE HEALTH SYSTEM

Effect of non-specific reversal agents on anticoagulant activity of dabigatran and rivaroxaban ***Thromb Haemost 2012;108:217***

A randomised crossover *ex vivo* study in healthy volunteers

Raphael Marlu[1]; Enkelejda Hodaj[2]; Adeline Paris[2]; Pierre Albaladejo[3,5]; Jean Luc Crackowski[2]; Gilles Pernod[4,5]

[1]Haemostasis Unit, University Hospital Grenoble, France; [2]Clinical Research Centre, INSERM CIC03, University Hospital Grenoble, France; [3]Department of Anaesthesiology, University Hospital Grenoble, France; [4]Vascular Medical Unit, University Hospital Grenoble, France; [5]Joseph Fourier Grenoble 1 University / CNRS TIMC-IMAG UMR 5525 / THemas, Grenoble, France



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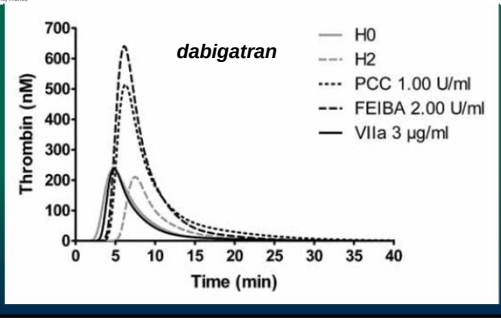


Safety of Recombinant Activated Factor VII in Randomized Clinical Trials

NEJM 2010;363:1791

Marcel Levi, M.D., Jerrold H. Levy, M.D., Henning Friis Andersen, M.Sc., and David Truloff, D.V.M.

Table 2. Odds Ratios for Thromboembolic Events.

Thromboembolic Event	rFVIIa (N=2583)	Placebo (N=1536)	Odds Ratio (95% CI)*	P Value
	number (percent)†			
All events	264 (10.2)	134 (8.7)	1.17 (0.94–1.47)	0.16
Arterial events	141 (5.5)	49 (3.2)	1.68 (1.20–2.36)	0.003
Venous events	137 (5.3)	88 (5.7)	0.93 (0.70–1.23)	0.61

* Odds ratios were calculated by means of logistic regression with adjustment for age and type of bleeding.
† The percentage of thromboembolic events was calculated as the number of patients with events as a proportion of the number of patients who received the assigned study drug.

Table 3. Arterial Thromboembolic Events with a Rate Greater Than 0.5%.

Variable	rFVIIa (N=2583)	Placebo (N=1536)	Odds Ratio (95% CI)*	P Value
	number (percent)			
All arterial thromboembolic events	141 (5.5)	49 (3.2)	1.68 (1.20–2.36)	0.003
Coronary events	76 (2.9)	17 (1.1)	2.39 (1.39–4.09)	0.002
Acute coronary syndromes	57 (2.2)	11 (0.7)		
Increased troponin level	19 (0.7)	6 (0.4)		
Cerebrovascular events	45 (1.7)	20 (1.3)	1.27 (0.74–2.17)	0.39
Cerebral infarction	44 (1.7)	19 (1.2)		
Hemiparesis†	1 (<0.1)	1(<0.1)		

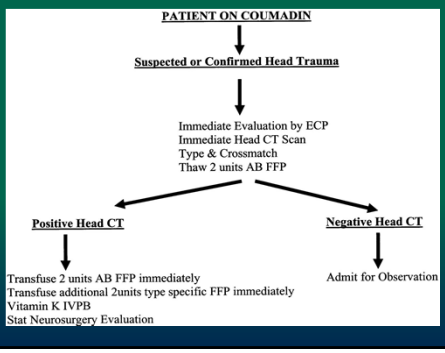
Strategies for urgent reversal

Strategies of urgent reversal of TSOACs

- **Drug removal from the circulation and/or gastrointestinal tract**
- **Pro-hemostatic therapies such as antifibrinolytic agents and DDAVP**
- **Prothrombin complex concentrates (PCCs), which may be prothrombotic**

"Coumadin protocol"

Ivascu, et al. J Trauma. 61:318-321, 2006.



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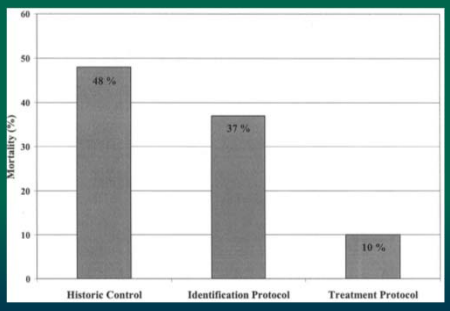


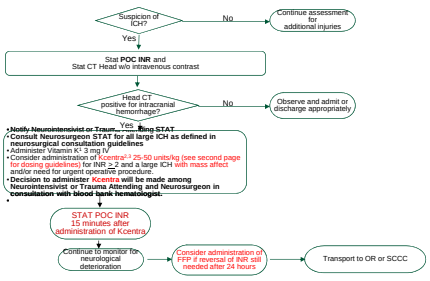
CHRISTIANA CARE HEALTH SYSTEM

Reversal of Warfarin in Patients with
Intracranial Hemorrhage (Traumatic and Non-Traumatic)

Trauma Department

POPULATION: All patients taking oral anticoagulants who have a suspected intracranial hemorrhage.

PURPOSE: To expedite the assessment and treatment of patients medicated with Warfarin who present with a suspected intracranial hemorrhage (ICH) with significant mass affect or requires urgent surgery.



[1]The risk of intravenous Vitamin K anaphylaxis should be explained to the patient and/or family when possible.
[2]The risk of clotting/thrombosis with the administration of Kcentra should be explained to the patient and/or family when possible.
[3]Generic Name: 4-factor PCC.

This guideline is to assist caregivers in the management of routine patients and should be modified for patient specific clinical indications.

Kcentra Dosing Guidelines (units/kg)

INR	Dose
2 - < 4	25 units/kg (max dose of 2500 units)
4 – 6	35 units/kg (max dose of 3500 units)
> 6	50 units/kg (max dose of 5000 units)

Kcentra Administration Guidelines

1. The Blood Bank technologist will provide the appropriate number of vials of reconstituted Kcentra intravenous administration.
2. Flush the intravenous site before and after administration with NSS.
3. Continuous transfusion of 0.12 ml/kg/min up to a max rate of 8.4 ml/min. (Refer to Formulary and Drug Therapy guide for more details.)
4. **Obtain a STAT INR 15 minutes after Kcentra is administered.**

Kcentra Hypersensitivity Reactions:

- **Acute headache, visual changes, pain in joints or muscles, respiratory difficulty, chills, back pain, dizziness, nausea or other unusual effects.** Discontinue infusion and notify the physician

Kcentra Relative Contraindications:

- Recent thromboembolic event (deep vein thrombosis, pulmonary embolus, myocardial infarction, stroke), DIC and known HIT.

Team Members * *Denotes Team Leader(s)*

Michael Lankiewicz, MD - Medicine/Hematology
Mark Cipolle, MD * - Trauma Director
Matthew Eppley, MD - Surgery/Neurologic Surgery
John Hays - Supervisor, Transfusion Services
Linda Laskowski Jones, ACNS-BC - Director, Trauma, Emergency & Aeromedical Services
Meredith Hollinger, PharmD - Clinical Pharmacy
Joan Pirung, ACNS-BC* - Trauma Program Manager
Thomas Scalea, MD - Epidemiology/Medicine

References

American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. (February 2012). Antithrombotic Therapy and Prevention of Thrombosis, 9th ED. Chest, 141(2).

Garra, G., Nashed, A.H., Capobianco, L., (1999) Minor head injury in anticoagulated patients. Academic Emergency Medicine, 6(2), 121-124.

Reversal warfarin related ICH at CCHS

- Notify neurointensivist or trauma attending STAT
- Consult neurosurgery for large hemorrhages as defined in consultation guidelines
- Administer 3mg vit K iv
- Consider administration of Kcentra (PCC-4) at doses of 25-50 units/kg (see next page)
- Decision to administer Kcentra will be made between neurointensivist or trauma attending and neurosurgery in consultation with blood bank hematologist
- Follow-up with POC INR 15min after completion of administration

Management of bleeding and reversal strategies for oral anticoagulants: Clinical practice considerations

Am J Hosp Pharm Nov 1, 2013

Edith A. Nutescu, William E. Dager, James S. Kalus, John J. Lewin III, and Mark D. Cipolle

Table 7.
Therapeutic Interventions for Reversal of Oral Anticoagulants Based on Urgency[12,15,16,18,19,45,46,66-69]

Level of Urgency	Warfarin	Dabigatran	Rivaroxaban or Apixaban
No rush (>24 hr)[a]	Withhold warfarin and consider oral phytonadione, with dose based on INR	Withhold drug and monitor clinical status and pertinent laboratory tests	Withhold drug and monitor clinical status and pertinent laboratory tests
Expedited (1–24 hr)[a]	Withhold drug and give oral phytonadione (1–5 mg) or low-dose i.v. phytonadione (0.25–5 mg), with dose based on initial INR and postreversal INR (checked 24 hr after dose)	Withhold drug, give activated charcoal[b] if last dose was taken within past 2 hr, and use prolonged hemodialysis (>2 hr)	Withhold drug and give activated charcoal[b] if last dose was taken within past 2 hr and repeat 6 hr after the last dose
Emergent (<1 hr)	Withhold drug, consider high-dose i.v. phytonadione[c] (depending on anticipated need to restart warfarin), and consider clotting factor supplement (listed in order of preference): • PCC4 • Build PCC4 with PCC3 plus rFVIIa[d] • aPCC • PCC3 • rFVIIa • FFP[e]	Withhold drug, give activated charcoal[b] if last dose was taken within past 2 hr, use prolonged hemodialysis (>2 hr), and consider clotting factor supplement (listed in order of preference): • aPCC • PCC4 • Build PCC4 with PCC3 plus rFVIIa[d]	Withhold drug, give activated charcoal[b] if last dose was taken within past 2 hr and repeat 6 hr after the last dose, and consider clotting factor supplement (listed in order of preference): • PCC4 • aPCC • Build PCC4 with PCC3 plus rFVIIa[d] • PCC3[f]

Urgent reversal - Warfarin

- Stop warfarin
- Oral or iv vit K (dose based on INR)
- PCC-4 (if available)
- PCC-3 + rFVIIa
- PCC-3 + FFP

Urgent Reversal - Dabigatran

- Stop drug
- Activated charcoal if < 2hours last dose
- “extended” hemodialysis
- Activated PCC
- PCC-4 or build a PCC-4 with PCC-3 + rFVIIa or FFP

Urgent reversal – Rivaroxaban/Apixaban

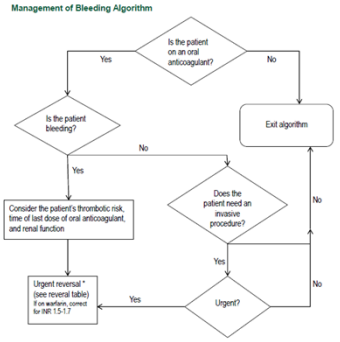
- Hold drug
- Activated charcoal if < 2hours last dose
- PCC-4
- Build a PCC-4 with PCC-3 + rFVIIa or FFP
- ? Activated PCC

CHRISTIANA CARE HEALTH SYSTEM
Care Management

Anticoagulation Reversal Guideline

Note: This guideline does NOT apply to patients in the Newborn Intensive Care Unit (NICU)

Management of Bleeding Algorithm



CCHS Oral Anticoagulant Reversal Guidelines

FOR THE BLEEDING PATIENT

*The intervention may need to be modified based on changes in the patient's clinical status (e.g., if status worsens, expedited or emergent treatment options should be considered). INR = international normalized ratio; PCC4 = four-factor prothrombin complex concentrate; FFP = fresh frozen plasma

‡Must consider patient's thromboembolic risk vs. benefit of reversal.

†Consider time of last dose and patient's renal function

Level of Urgency	Warfarin	Dabigatran	Rivaroxaban	Apixaban
Emergent (reversal needed < 1hr)* Examples may include: • CNS bleeds (IPH >2cm, cerebellar) • GI bleeds (hemorrhage with shock or with Hgb. < 7) • Trauma (solid organ injury >1) • Epistaxis (fails basic packing) • Retroperitoneal hematoma (hemorrhage with shock)	- Withhold drug - Consider 5-10mg IV phytonadione (vitamin K) - Consider PCC4 (Kcentra)‡ INR Dose 2 - < 4 25 units/kg (max= 2500 units) 4 - 6 35 units/kg (max= 3500 units) >6 50 units/kg (max= 5000 units) (If given, administer Vitamin K concurrently to maintain factor levels once the effects of PCC4 have diminished)	- Withhold drug† - Consider activated charcoal if last dose within 2 hours - Consider prolonged dialysis (up to 60% of drug removed) - Consider PCC4 (Kcentra) 25 units/kg; max = 3500 units	- Withhold drug† - Consider activated charcoal if last dose within 2 hours and repeat 6 hours after the last dose - Consider PCC4 (Kcentra) 25 units/kg; max = 3500 units	- Withhold drug† - Consider activated charcoal if last dose within 2 hours and repeat 6 hours after the last dose - Consider PCC4 (Kcentra) 25 units/kg; max = 3500 units
Non-urgent*	- Withhold drug - Lower or omit dose - May consider FFP (if reversal required between 1 and 24 hours) - Consider 1 to 5mg PO phytonadione (Vitamin K) with dose based on initial INR and post reversal INR (checked 24hr after dose) - Consider 2.5 to 5mg PO phytonadione (Vitamin K) if INR > 5 and insignificant bleeding	- Withhold drug and assess renal function to determine half-life of drug† - Consider activated charcoal if last dose within 2 hours - Consider prolonged dialysis (up to 60% of drug removed)	- Withhold drug and assess renal function to determine half-life of drug† - Consider activated charcoal if last dose within 2 hours and repeat 6 hrs after the last dose	- Withhold drug and assess renal function to determine half-life of drug† - Consider activated charcoal if last dose within 2 hours and repeat 6 hours after the last dose

CHRISTIANA CARE HEALTH SYSTEM

Anticoagulation Inpatient Guideline

Care Management

POPULATION: All patients admitted on an anticoagulant and/or antiplatelet medication in the setting of a bleeding event
PURPOSE: To improve the clinical outcomes for patients on anticoagulants and/or antiplatelets

Care Guidelines

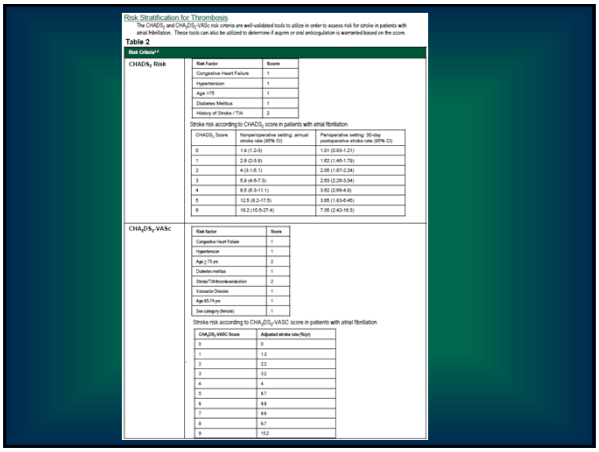
Anticoagulant / Antiplatelet medications should be interrupted only if the provider feels it is necessary. Even temporary interruption can result in increased cardiovascular or neurovascular risk for MI or stroke. To determine the necessity of interruption, a collaborative discussion between providers is recommended.

Determining the indication for these medications will help to determine the appropriate time frame for withholding therapy. Examples of indications are included in Table 1.

Do not restart anticoagulation if patient has an indwelling epidural catheter.

Medication	Indication(s)
Aspirin	Acute Coronary Syndromes (ACS) Atrial Fibrillation Coronary Artery Bypass Graft (CABG) Carotid Artery Stenosis Coronary Artery Disease Peripheral Artery Disease Primary Prevention Ischemic Stroke/Transient Ischemic Attack (TIA) Intracranial Stents Dissections: carotid or vertebral arteries
Clopidogrel (Plavix)	ACS Atrial Fibrillation CABG Percutaneous Coronary Intervention (PCI) Intracranial Stents Dissections: carotid or vertebral arteries
Prasugrel (Effient)	PCI for ACS Intracranial Stents
Ticagrelor (Brilinta)	ACS Intracranial Stents
Warfarin	Atrial Fibrillation Coagulation Disorders (ex: Antiphospholipid Syndrome, Proteins C and S deficienc Prosthetic Valve Venous thromboembolism (VTE) Dissections: carotid or vertebral arteries
Dabigatran (Pradaxa)	Nonvalvular Atrial Fibrillation
Rivaroxaban (Xarelto)	Nonvalvular Atrial Fibrillation Venous Thromboembolism
Apixaban (Eliquis)	Nonvalvular Atrial Fibrillation

ideline is to assist caregivers in the management of routine patients and should be modified for pat



Risk Stratification for Thrombosis

The $CHADS_2$ and CHA_2DS_2-VASc risk criteria are well-validated tools to utilize in order to assess risk for stroke in patients with atrial fibrillation. These tools can also be utilized to determine if aspirin or oral anticoagulation is warranted based on the score.

Table 2

Risk Groups[1]

$CHADS_2$ Risk

Risk Factor	Score
Congestive Heart Failure	1
Hypertension	1
Age ≥75	1
Diabetes Mellitus	1
History of Stroke / TIA	2

Stroke risk according to $CHADS_2$ score in patients with atrial fibrillation

$CHADS_2$ Score	Nonperioperative setting: annual stroke rate (95% CI)	Perioperative setting: 30-day postoperative stroke rate (95% CI)
0	1.9 (1.2-3)	1.01 (0.63-1.21)
1	2.8 (2.3-3)	1.62 (1.48-1.79)
2	4 (3.1-5.1)	2.05 (1.87-2.24)
3	5.9 (4.6-7.3)	2.63 (2.26-3.04)
4	8.5 (6.3-11.1)	3.62 (2.89-4.6)
5	12.5 (8.2-17.5)	3.65 (1.83-6.45)
6	18.2 (10.5-27.4)	7.35 (2.43-16.3)

CHA_2DS_2-VASc

Risk factor	Score
Congestive Heart Failure	1
Hypertension	1
Age ≥ 75 yrs	2
Diabetes mellitus	1
Stroke/TIA/thromboembolism	2
Vascular Disease	1
Age 65-74 yrs	1
Sex category (female)	1

Stroke risk according to CHA_2DS_2-VASC score in patients with atrial fibrillation

CHA_2DS_2-VASC Score	Adjusted stroke rate (%/yr)
0	0
1	1.3
2	2.2
3	3.2
4	4
5	6.7
6	9.8
7	9.6
8	6.7
9	>9.2

Table 3.

Risk Stratum for Thrombotic Events[3,4]	Indication for Anticoagulant Therapy		
	Mechanical Heart Valve	**Atrial Fibrillation**	**VTE**
High Risk	Any mitral prosthesis Any caged-ball or tilting disc aortic valve prosthesis Recent (within 6 mo) stroke or TIA	$CHADS_2$ score of 5 or 6 Recent (within 3 mo) stroke or TIA Rheumatic valvular heart disease	Recent (within 3 mo) VTE "Severe" thrombophilia*
Moderate Risk	Bileaflet aortic valve prosthesis and ≥ 1 of the following risk factors: Atrial fibrillation, prior stroke or TIA, hypertension, diabetes, CHF, age > 75	$CHADS_2$ score of 3 or 4	VTE within past 3-12 mo Recurrent VTE Active cancer (treated within 6 mo or palliative) "Nonsevere" thrombophilia†
Low Risk	Bileaflet aortic valve prosthesis without atrial fibrillation and no other risk factors for stroke	$CHADS_2$ score of 0 to 2	VTE > 12 mo previous and no other risk factors

Table 4.

Type of bleed	When to resume: Need to assess indication for use, risk for thrombosis, and risk of clinically significant rebleeding. If patients are on aspirin only for primary prevention of atherosclerotic events, it is reasonable to stop aspirin until the bleeding event is completely treated. NOTE: Unless referenced, the basis of these recommendations is expert consensus.	
	Anticoagulant	Antiplatelet
Gastrointestinal Bleed Hematochezia Melena Hematemesis	Full anticoagulation should be resumed after bleeding stopped based on thrombotic risk: High risk- within 4 days[5] Moderate risk- within 1-2 weeks Low risk – Consider within 2-4 weeks NOTE: Endoscopic evaluation and therapy in the setting of acute bleeding can be safely performed with an INR < 2.5.[9]	Withhold dual antiplatelet therapy (DAPT) for 24 hours to assess bleed[6,8] For all patients on aspirin for indications listed in Table 1, we recommend resuming aspirin (81mg) within 24 hours, or potentially continuing aspirin without interruption For patients with a DES <12 mo, BMS <3 mo, or intracranial stent <12 mo--restart second agent within 1-2 weeks Add acid suppressants ie PPI, should be part of therapy

CCHS AC and AT Resumption

Trauma	Full anticoagulation should be resumed after bleeding stopped based on thrombotic risk: High risk- within 4 days[5] Moderate risk- within 1-2 weeks Low risk – Consider within 2-4 weeks	Withhold dual antiplatelet therapy (DAPT) for 24 hours to assess bleed For all patients on aspirin indications listed in Table 1, we recommend resuming aspirin (81mg) 24 hours after bleeding stops For patients with a DES <12 mo, BMS <3 mo, or intracranial stent <12 mo--restart second agent within 1-2 weeks
Intracranial or intraspinal hemorrhage : Traumatic and Spontaneous	Trauma: Re-evaluate reason for anticoagulation: Antithrombotics vs Antiplatelets Anticoagulation should be resumed after bleeding stopped based on thrombotic risk: High risk- resume 7-10 days after bleeding event Moderate risk- resume within 2-3 weeks Low risk – resume within 3-4 weeks Spontaneous: -Identify/Secure underlying lesion: aneurysm/AVM *Neurologic consultations prior to re-initiation of full anticoagulation	Trauma: Withhold dual antiplatelet therapy (DAPT) for 24 hours to assess bleed For all patients on aspirin indications listed in Table 1, we recommend resuming aspirin (81mg) Small bleeds: within 48 hours if neuro exam and CT stable or improved for small bleeds Large bleeds: Hold aspirin for 5 days For patients with a DES <12 mo, BMS <3 mo, or intracranial stent <12 mo--restart second agent within 1-2 weeks Spontaneous: Identify/Secure underlying lesion: aneurysm/AVM For patients with a DES <12 mo, BMS <3

Summary

- A PCC-4 was as effective in providing hemostasis, and was faster at correcting INR, compared to FFP in a recent phase 3 trial
- There are currently NO data to guide us in urgent reversal of anti-platelet agents
- Prothrombin complex concentrates, either 4 factor or activated, are showing “promise” in reversing the new anticoagulants
- Antidotes and monoclonal antibodies are being developed for reversal
- Your institution should have a multidisciplinary strategy for urgent reversal of all anticoagulants based on the best available data
- Must “choose wisely” when considering resumption of AC or AT